Antipsychotics – Risk stratification table

General information

- First and foremost, **preventing delirium should be a priority** by providing appropriate pain management, maintaining a regular sleep cycle and closely monitoring for infections, constipation and dehydration.
- It may be more appropriate to discontinue some medications rather than adding them if patients are delirious.
- The treatment of delirium focuses on addressing **the symptoms of delirium** such as delusions and hallucinations that cause fear, anxiety, distress and discomfort while identifying and treating the underlying source of the delirium and treating it.
- **Medication is never the first choice** and should only be administered to alleviate the symptoms if the patient poses a threat to himself or others and documented nonpharmacological options (e.g., behavioral interventions) have failed (57).
- **Always start with the lowest effective dose** when treating delirium with antipsychotics (57).
- There are limited resources available for treating delirium, and medications used to treat delirium do not significantly impact the length of hospital stay or the duration of delirium.
- Generally, no medications are used to treat hypoactive delirium
- When most antipsychotics are used together with medications with CNS depressant effect it may impair the ability to perform dexterity tasks (24).
- Most antipsychotics can **cause prolongation of the QTc interval**, the 1st generation antipsychotics are at higher risk, and they may also **increase the risk of EPS.**

Medication	Route of administration	Typical dosing range	Mechanism of action	Special considerations	References
Haloperidol (Haldol®) 1st generation	PO, IM & IV	0,5-5 mg/day	Potent D2 blockade Minimal Sedation Metabolized by CYP3A4 and CYP2D6 $T_{1/2}$: 24h	Considerations: **FDA warning for QTc prolongation for IV form** **High risk of increased extrapyramidal side effects** May cause encephalopathy, neuroleptic malignant syndrome and acute brain syndrome if combined with lithium. Pharmacokinetics can significantly change if co-administered with carbamazepine. Avoid oversedation Treatment of delirium: Usually the **first drug of choice** to treat delirium, particularly in hyperactive delirium for sedation and in seriously ill patients. **Use with caution at lower doses for a short duration of time** Avoid in treatment of mild delirium in palliative care patients. **Olanzapine can be a safe alternative for patients with delirium in the ICU**	1, 2, 4, 5, 6, 7, 10, 11, 12, 13, 14, 16, 18, 19, 23, 50, 51, 56, 59, 61, 62, 67, 72, 81, 82, 87, 88, 90, 92, 94, 95, 98, 100, 107, 109

Quetiapine (Seroquel®) **2nd generation** 	PO	12,5- 50 mg/day	Minimal D2 blockade High sedation Metabolized by CYP3A4 $T_{1/2}$: 6-7h	Considerations: Metabolic side effects and orthostatic hypotension Reaches a peak plasma concentration 1,5h after administration Treatment of delirium: Off-label for the management of delirium **as an anxiolytic for ventilated patients in the ICU setting.** Used as prevention and treatment of postoperative delirium **Preferred over haloperidol if extrapyramidal symptoms are present** Sometimes recommended in delirium when the sleep cycle is interrupted	3, 8, 9, 15, 19, 46, 75, 85, 87, 88, 89, 93, 96, 100, 101, 102, 103, 105, 108, 110
Olanzapine (Zyprexa®) (Zalasta®) **2nd generation** 	PO, IM & IV	2,5-10 mg/day	Moderate D2 blockade Moderate sedation Metabolized by CYP1A2 $T_{1/2}$: 30h	Considerations: Metabolic side effects, dizziness and reduced blood pressure Possible cerebrovascular events in the elderly In the case of sepsis, medication concentration and duration can increase Risk of inducing or worsening delirium, especially at high doses Not recommended for Parkinson's patients Treatment of delirium: Treatment option in perioperative settings **Effective for critically ill patients with delirium** Has been used in the ICU to treat delirium when treatment with haloperidol is unsuccessful May be used in the treatment of delirium in patients experiencing extrapyramidal symptoms in the lowest dose Highest anticholinergic effects among all antipsychotics used for postoperative delirium **Should not be used in hypoactive delirium**, as it is a very sedative drug	13, 15, 18, 20, 21, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 55, 56, 57, 58, 60, 63, 64, 66, 70, 73, 74, 77, 83, 84, 85, 91, 93, 97, 101, 104, 106, 108, 109
Aripiprazole (Abilify®) **2nd generation**	PO & IM	5-10 mg/day	Partial agonist on D2 and 5-HT Lack of sedative property Metabolized by CYP3A4 and CYP2D6 $T_{1/2}$: 75h	Considerations: Akathisia, diabetes, anxiety and restlessness Might cause serotonin syndrome Acute confusion may occur in case of an overdose Treatment of delirium: Not used to treat delirium in practice **Option for delirium patients who do not require substantial sedation.** Might be promising in hypoactive delirium treatment	11, 14, 17, 19, 24, 25, 26, 27, 28, 29, 30, 60, 64

Risperidone (Risperdal®) (Rison®) **2nd generation**	PO	0,5-16 mg/day	High D2 and 5-HT blockade Mild sedation Metabolized by CYP3A4 and CYP2D6 $T_{1/2}$: 3-20h	Considerations: Nausea, upper abdominal pain and dizziness Increases the risk of stroke and can cause neuroleptic malignant syndrome and drug hypersensitivity (rare) Can cause confusion, extreme excitement and hallucination Reaches peak serum concentrations in 1–2h Treatment of delirium: Not used to treat delirium in practice **Avoid use for treatment of mild delirium in palliative care patients**	14, 18, 47, 48, 49, 56, 57, 60, 64, 72, 80, 84, 86, 101
Ziprasidone (Zeldox®) **2nd generation**	PO, IM & IV	20-160 mg/day	Moderate D2 blockade Mild sedation Metabolized by CYP3A4 $T_{1/2}$: 7h	Considerations: Insomnia, somnolence, headache and agitation **Conflicting association with QTc prolongation** Treatment of delirium: Not used to treat delirium in practice May be used in postoperative delirium with the **lowest effective dose**	4, 14, 15, 19, 89
Chlorpromazine (Largactil®) **1st generation**	PO, IM & IV	25-100 mg/day	Blocks a variety of receptors High sedation $T_{1/2}$: 6h	Considerations: Can enhance extrapyramidal symptoms **High-risk medication for inducing or worsening delirium**, especially in postoperative settings, palliative and critical care Commonly used in perioperative settings that might induce postoperative delirium and should be avoided Treatment of delirium: Not used to treat delirium in practice **Not routinely used and should be avoided**	54, 55, 57, 58, 59, 61, 63, 65, 66, 68, 69, 70, 71, 78, 81, 83, 93, 99, 101
Levomepromazine (Nozinan®) **1st generation**	PO, IM & IV	5-25 mg/day	Antagonistic effect on D1 and D2 High sedation $T_{1/2}$: 15h	Considerations: Early dyskinesia with spastic torticollis and eye movement disorders Increased risk of neuroleptic malignant syndrome if combined with other antimuscarinic agents Very anticholinergic **May induce delirium**, commonly in palliative medicine Treatment of delirium: Not used to treat delirium in practice **Avoid use**	19, 22, 60, 64, 76

Clozapine (Zaponex®) 2nd generation	PO	6,25-25 mg/day	Antagonistic effect on D2 and 5-HT High sedation Metabolized by CYP1A2 $T_{1/2}$: 12h	Considerations: Agranulocytosis, seizures, cardiovascular events and fever Risk of malignant neuroleptic effects if combined with CNS depressants or lithium **Requirement for monitoring full blood counts** Can increase effects of CNS depressants Delirium, hallucinations and confusion in case of an overdose, especially in vulnerable patients (elderly and patients on anticholinergics) **Risk of inducing or worsening delirium and confusion** Treatment of delirium: Not used to treat delirium in practice **Deprescribing and/or avoid use**	3	21, 31, 32, 52, 53, 55, 57, 60, 79

Can be used for Parkinson's patients

Do not use in Parkinson's patients

High risk of constipation that can induce delirium

1 2 3 The anticholinergic burden score

Use with caution in liver-impaired patients who might require dose adjustment

Use with caution in kidney-impaired patients who might require dose adjustment

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